The Research Council of Norway

Evaluation of the Centre for Molecular Medicine – NCMM

Report of the Evaluation Committee

The Research Council of Norway
P.O.Box 2700 St. Hanshaugen
N–0131 OSLO
Telephone: +47 22 03 70 00
Telefax: +47 22 03 70 01
bibliotek@rcn.no
www.rcn.no/english

The report can be ordered at:
www.forskningsradet.no/publikasjoner

or green number telefax: +47 800 83 001

Oslo, August 2013

ISBN 978-82-12-03237-8 (pdf)

Table of Content

Evaluation Report – Centre for Molecular Medicine - NCMM

• Executive Summary

The Centre for Molecular Medicine Norway (NCMM) was created as partnership between Nordic Academic institutions and the European Molecular Biology Laboratory (EMBL). The NCMM was created in 2007 with the ambition to capitalise on Norway's strengths in cancer, cardiovascular, inflammatory and CNS-related diseases. The project has a clear mission to establish an internationally recognised translational research centre, while maintaining a high level of scientific excellence. The Evaluation Committee (commissioned by the Research Council of Norway, RCN) has had the opportunity to review the mid-term report filed by the 8 group leaders working at NCMM. Materials requested by the Committee provided additional information relating to the translational research activities, access and use of core facilities and attention to gender issues during the recruitment of Group Leaders. A site visit of the NCMM and a full day of scientific presentations and discussions with the various stakeholders further informed the committee (agenda for the site review is provided as an Annex).

Overall, the Committee was impressed by the early success in establishing the NCMM and believed that the investigators recruited will help realise the stated institutional mission. The NCMM is efficiently organised and expertly managed by the NCMM director, who is to be congratulated on the job he has done in the first few years. There appears to be significant collaborations and access to key facilities between NCMM and the neighbouring Biotechnology Centre of Olso (BiO). The Scientific Advisory Board (SAB) has participated in two reviews of the NCMM and the Committee agreed with many of their observations. NCMM core funding totals 27M NOK (~3.6M Eu), coming from the three stakeholders (RCN, UiO and Health South East, HSE). It is clear that continued support is required in order to fulfil the stated goals of the NCMM and maintain its' tripartite mission of scientific excellence, training and delivery of solutions for high priority medical needs.

As a summary of the Committee's assessment, we wish to highlight:

(1) The recruitment of excellent young group leaders, with the ambition to contribute to Norway's next generation of leaders in Life Science Research;
(2) The commitment to translational research that is exhibited by each group leader, and the unique training environment that NCMM offers to PhD and MD students, junior investigators and clinicians; and
(3) The importance of establishing a strategic direction regarding the next phase of NCMM growth and development, paying particular attention to (i) ensuring proper mentorship of the junior investigators, (ii) consolidating the bi-lateral transfer of information, expertise and knowledge from the laboratory to clinic, and (iii) stabilise what remains a nascent community of scientists, students and clinicians.

In sum, the committee offers its resounding support for continuation of RCN funding, and hope that the other stakeholders will act similarly, noting that excellent early progress has been made. It is still early days, but in accordance with the request from the RCN, we rank the Centre with an overall score of *Very Good* with the potential to achieve *Excellent* in the coming years. Specific recommendations are provided below. Further investment would consolidate early success and permit the building of greater critical mass in strategic areas.

• Evaluation Committee

Matthew L. Albert, MD PhD (chair). Dir Dept of Immunology, Institut Pasteur
Margaret Frame, PhD. Research Dean, College of Medicine, Edinburgh, and Director, Edinburgh Cancer Research Centre
Thomas Perlmann, PhD. Dir of Ludwig Institute for Cancer Research, Stockholm Branch, Karolinska Institute
Rosa Barreira de Silva, PhD. (scientific secretary)
Iain Mattaj, Director General EMBL (observer)
[Biographical information on committee members is provided as in annex.]

Evaluation of the Centre

The Centre for Molecular Medicine Norway (NCMM) is a biomedical research institute with the stated objective being a centre of excellence for the recruitment of new outstanding group leaders and for promoting the translation of basic medical research into clinical practice. Cancer, cardiovascular disease, inflammatory and CNS-related diseases have been prioritised, serving to strengthen Norway's strategic position in these areas of research. The NCMM also aspires to establish new diagnostic methods and define drug targets, as well as adapt medical technologies for personalised medicine strategies. Situated within Oslo Research Park and partnerships with the BiO and the Centre for Molecular Biology and Neuroscience, is meant to facilitate research activities and support commercial exploitation of NCMM activities.

The NCMM was launched with 3 founding groups (Taskén, Ottersen/Amiry-Moghaddam, Krauss) and during the first five years has recruited 5 independent group leaders (Hurtado, Mills, Morth, Nagelhus, and Staerk). The NCMM is headed by Taskén who also directs the neighbouring BiO. A local Board, composed of representatives from the stakeholder institutions helps to coordinate activities of the NCMM.

A stated objective of this evaluation is to provide data to advise on the decision as to whether to continue the NCMM allocation for a new 5-year period. The NCMM is still in its infancy and given the broad and ambitious goals for the institution, the answer to the question of "continued funding" was unanimously positive. In fact, we recommend an augmentation of funds, which could be used to consolidate early success and ensure continued growth of the NCMM, thus permitting them to achieve increased international visibility.

A. Strategic role and development of the centre

The evaluation is expected to assess to what extent the following:

• The EMBL partnership facilitates access to scientific infrastructure, including databases, facilities and instrumentation, as well as access to clinical materials, services and training activities provided by each of the partners

There is clear evidence that the partnership offers the possibility to access leading-edge technologies and build collaborations with clinical investigators. For a few of the groups, these opportunities have been exploited (e.g., access to the beam line for crystallographic work). It may be premature to evaluate newer groups that are still in the process of establishing themselves. What should be considered is which of these activities could have been accessed without a formal EMBL partnership. What was evident from the committee's review is the commitment of the EMBL leadership that the Nordic partners succeed, and help realise their vision of hiring and nurturing young group leaders. Specifically, the EMBL has helped define a strategy that has a proven record for the identification and recruitment of outstanding group leaders at EMBL. Moreover, it was beneficial that EMBL participated in the hiring of new group leaders, and this should be continued during the next round of recruitments. The students appreciated the meeting in Barcelona with the other Nordic EMBL partners. EMBL also profits from the opportunity to interact more with its member states in the Nordic region. One challenge for the NCMM is to start contributing to the EMBL infrastructure (e.g., bioinformatics tools, databases), helping to create more visibility for the NCMM and "paying back" to the partner institutions. For the EMBL, they can support the NCMM by providing greater visibility on their home page (EMBL.org) with an easy link to EMBL partnerships (rather than embed the link within Heidelberg Research activities).

• The Nordic partnership has built on and exploited the strengths in all three partner institutes.

This is an exciting opportunity, and early indications look promising. Certainly, the promise and opportunity for true partnership among the Nordic EMBL associated institutes (Norway, Sweden, Finland and now Denmark) provides a foundation for building joint training programs, sharing of infrastructure and core facilities, and possibly the execution of multi-national clinical studies. The committee supports the continued commitment to the EMBL model, promoted by integrated

international PhD and MD/PhD programs. Specific examples of collaborations and shared training are discussed below.

• The centre is able to counteract fragmentation and build critical mass

The committee spent some time trying to define "fragmentation" as it applies to Norwegian life sciences. In fact, we identified several states of affairs that are fragmented about life sciences in Norway: (i) funding opportunities are seemingly random with Centres of Excellence appearing and disappearing on a 10yr cycle; (ii) training program is split across several Centres with no coordination of mentorship and training of young scientists; (iii) core technologies, while exceptional, are located within individual laboratories rather than integrated Technical Platforms with engineering support and institutional commitments for maintenance and modernization of the instrumentation; (iv) identity and institutional allegiance for investigators is a challenge, with one of the NCMM investigators currently having five affiliations. If the ambition is for the NCMM to unify different life sciences opportunities, then additional resources, space and a clearer mandate is required.

With respect to the question of critical mass, NCMM is a small Centre. It has made impressive strides towards addressing the critical need for recruiting young group leaders from overseas. Given that the criteria was scientific excellence, NCMM succeeded in recruiting 5 early stage career group leaders with distinct, but overlapping research interests. Ideally, the committee would like to see additional recruitment in the form of 1-2 senior investigators. All future recruitments should be in strategic areas that will reinforce the current scientific themes covered by the NCMM.

• The centre has been able to attract and recruit outstanding younger scientists within molecular medicine nationally and from abroad

This has been a major accomplishment and has helped install an essential mechanism for establishing the highest level of life science research in Norway. Some challenges remain, and there is an unmet need for mentoring the recruited younger scientists. Specifically, they need to be encouraged and supported in their applications for extramural funding and an environment fostered to optimise scientific and translational output. Of note, OiU investigators have been successful in obtaining 10 ERC grants (some of which are in the area of life sciences,), but none have so far come from the NCMM group leaders.

• The centre has been successful in developing infrastructure to facilitate translation of discoveries in basic medical research into clinical practice

The international recruitment of new group leaders has led the NCMM to develop infrastructure – e.g., structural biology, ChIP sequencing and generation of human induced pluripotent stem (iPS) cell lines. The facilities were funded from multiple sources, and were excellent and appropriate to facilitate the pursuit of translational ambitions of the NCMM.

• The centre has exploited national scientific strengths

With the support and guidance from EMBL, the NCMM is helping to raise the bar for recruitments in Norwegian life sciences. The Associate Investigator program has helped to integrate the NCMM within the frame of current Norwegian activities, and while there are relatively modest gains for the associated faculty at present, the fact that applications are submitted to the annual competitive call suggests it is of attractive to be an Associated Member of the NCMM. Several investigators take advantage of National resources (e.g., HSA Biobanks, Norwegian sequencing facility and others).

• The centre has contributed to training activities and competence development

The committee saw visible evidence of excellent training opportunities, and NCMM has had a positive influence on life sciences training and competence development. This can be measured in the number of new young group leaders and the PhD / post-doctoral fellows being trained in their respective laboratories. Additionally, the committee was impressed (and at times envious) of the excellent technical and screening competence that has been established over the last five years. It will be important for the NCMM stability and visibility to determine what it (as an institute) wants to "brand" as NCMM. The committee recommends that the institute take increasing ownership (if possible with Oslo University) of PhD programs and early career development. This will help establish a stronger community of scientific excellence and help the students feel they belong to the NCMM.

One area that requires serious consideration is the need for new capacity development in the areas of statistics, bioinformatics and computational science. This may be a priority for new recruits. EMBL could help here, as it is well positioned to support the recruitment of a top computational biologist that can lead his/her own research program and support the ongoing work of younger reserachers. As a second priority, the committee suggests strengthening ties to medicinal chemists, who can support exploitation of small molecule screening and clinical testing.

• The centre has enhanced collaboration with biotechnology and bio-pharmaceutical industries

It is early days to evaluate this criteria. All new investigators appear open to partner with industry and biotechnology companies. There is evidence of fledgling pharmaceutical alliances and collaboration, particularly involving the founding partners.

• The centre has established new contacts and created new research networks beneficial for national and international research within its field.

Investigators at the NCMM aspire to develop strong national and international collaborators through networking, and there was evidence this was beginning. There were some examples of EU FP7 partnerships and consortia building. In the coming years, NCMM should have leadership roles in disease-focussed clinical research – this may be an area where HSE can offer some additional support and guidance. Again, the founding partners (in particular the NCMM director) are well connected, playing an important role in EATRIS and EU-OPENSCREEN. It was difficult to establish which activities are being led by associated institutes or centres (e.g., UiO, BiO), and which are a direct result of investment in NCMM. Additional networking will undoubtedly follow (and is encouraged), especially with the growing investment in translational research at the European level (e.g., IMI).

• The scientific leadership is being exercised in an appropriate way, at both centre and group level

The Centre director can be justifiably proud of all that has been accomplished during the past five years. The NCMM is off to a great start and it has succeeded in a big way, with respect to the recruitment of international, young scientists as independent investigators. While the committee recognised the strong leadership of the director, we were concerned that he is on his own and very busy. As a result, some things have clearly fallen through the cracks. As detailed in other sections of this evaluation, stronger on-going mentoring and career development is required for group leaders and early career researchers. We were somewhat surprised by the small number of students or postdoctoral fellows (2 of 18) that expressed a strong commitment to emerging as a group leader and head of an academic laboratory. It was unclear what the others are planning to do with their career. The need for additional support at the senior level was evident from the heterogeneous style and presentation of the self-assessment reports. Appointment of additional senior scientists would provide additional leadership support that would help the Director and ensure success of the NCMM.

• The centre's activities and organization contribute to the aim of being a national resource centre

The committee recognised the recruitment of excellent early career researchers as being a first step towards the goal of being a national resource. This cannot however be the endpoint, as the group leaders will only be transiently associated with the NCMM (as per EMBL staffing principles). Thought needs to be given by all parties to what happens to these investigators once their NCMM tenure is over. It is also an important part of the next phase for NCMM that national and international visibility is enhanced, for example by bioinformatics and computational capacity building, NCMM-led symposia and NCMM-labelled training activities that will advance the mission of bridging basic and clinical research activities locally and internationally. Gaining traction as a leading institution on the world stage will take time, but will further the goals of being a national resource centre.

B. Research plans for the next five-year period

• Scientific plans and priorities for providing science with high scientific impact and relevance with respect to the centre's goals

As for any aspiring internationally-leading Centre, attention needs to be paid to achieving high-impact scientific publications as it is the currency of scientific success. The strategy has been to appoint early career investigators with high potential, let them lead their science strategies in an appropriate environment. It is too early to judge whether high impact science and publications will emerge from work done after their arrival at the NCMM. The 'achievement' goals would benefit from additional senior staff fully engaged in the NCMM and ready to help support success of junior group leaders.

• Recruitment and training

No plan was presented for further recruitment; there may be a problem with the 5+5yr cycle of funding. For example, is it the case that if the NCMM recruits an investigator at year 7, they will have 3yrs but not 5yrs of committed money? This question (and potential problem) needs to be considered by the funders, as it will create difficulties if the NCMM is not able to continue recruitment over the next 5yrs. The committee suggests growing the Centre over the next five years (numbers depend on the potential merger with BiO) if it wishes emerge as a leading internationally recognised Centre. This will aid sustainability, and ensure continuity of scientific staff when the current crop of young investigators leave the NCMM at the end of their tenure (which may happen early as they take up more permanent posts). A staggered recruitment scheme for young investigators is necessary to achieve a vibrant and sustainable centre of excellence (built on the EMBL model).

A key part of any research Centre is the organization of NCMM-led training for students and post-doctoral fellows, with a good proportion aspire to become a future research leader. The NCMM should give attention to organising complementary, inter-disciplinary training activities that will help trainees to know their options and empower them to make key longer-term choices, armed with the necessary information about the range of career choices in life sciences.

• Collaboration and synergy between centre groups

Collaborations and collegiality between group leaders seemed good. Care should be taken with those laboratories not presently located within the NCMM space, as they may become 'disconnected'.

• Collaboration nationally/internationally/with EMBL-partners, including basic and clinical collaboration

Collaborations seem to be in place; these are based on scientific need and a true desire to collaborative regarding patient cohorts relevant to the diseases being studied by NCMM researchers. There is also evidence of collaborations being developed between the Nordic EMBL partners, and this is expected to build over the coming years. This should be organic, investigator initiated and based on shared scientific priorities and scientific goals. One obvious place for strong collaboration would be the creation of shared training opportunities and courses (e.g., EMBO courses) for associated students and early career scientists. The partnership with EMBL has been valuable in regard of support and advice for recruitment of group leaders to the NCMM, The committee would like to have seen more evidence of interactions with EMBL scientists post appointment.

• Strategies for innovative findings of commercial interest

Intellectual property of the NCMM investigators is owned and controlled by UiO. As such, the investigators are dependant onUiO technology transfer. Synergy with the grants support and technology transfer office is obviously a high priority as major European funding initiatives now insist on partnerships between academic institutes and businesses.

C. Specific recommendations

The committee has organised specific recommendations into three categories.

• Long-term vision and investment in NCMM as a lead institution for Norwegian Life Sciences
The NCMM and the stakeholders should be congratulated for their commitment to improving scientific excellence and translational research in Norway. While success to date is evident, there will be additional investment and work required to create a sustainable research Centre. Critically, there needs to be further recruitment of a strategic nature, and if possible, one or two senior investigators to ensure balance and experience aid the director in achieving NCMM goals. The committee noted the lack of 'participation' by two of the three founding members and suggest that the current "founding members" be instead considered as "associate members."

To achieve greater international visibility, it is important that the NCMM identify means of continuing to recruit new group leaders. The next hires should be strategic recruitments, helping to consolidate research efforts, given there is a diverse set of research programmes (for a small cohort of principal investigators) within the centre. Additionally, long-term strategic planning is required, and should be discussed with funding partners, in order to establish a mechanism for key investigators to remain active members of the NCMM community once they leave (assuming they remain local).

• Investment in NCMM infrastructure, training and support for Translational Research
The committee was highly impressed by the investment in technologic systems for neuro-imaging, medium-throughput ChIP, and small molecule screening/peptide mapping. To fully realise the potential presented by this investment, it is important that NCMM core facilities are made available to the greater Norwegian life science community (with a proper charging structure). In addition to the technical aspects of discovery research, further investment in the area of bioinformatics and computational science is recommended.

The committee recommends that the NCMM increases ownership of its PhD training program (if possible), with the establishment of thesis committees, and some formal mentoring. Greater attention to the career development of PhD and post-doctoral fellows is advised. We also recommend better exchange between clinical and basic researchers, for example by establishing a medical education seminar series that will highlight its commitment to delivering information, expertise and new tools / treatments for managing patients. Given the extensive collaborations between clinical teams and NCMM investigators, this could be initiated with a focus on the current projects and extended to new high-priority areas as a means of inspiring new interactions and partnerships in clinical translational research.

D. Scientific quality of the research

Founding group - Signalling networks in health and disease

- ***Short description of the group (facts and organisation)***

This group is focused on the understanding of intracellular signalling pathways: the A-kinase anchoring proteins (AKAPs) and cAMP-regulated signalling pathways; and how these contribute to immune regulation and disease pathogenesis. Applying a combination of discovery- and hypothesis-driven research, the group examines a broad spectrum of diseases, ranging from HIV disease to tumour immunity. The group currently consists of 3 senior staff, 7 post-docs, 4 PhD students, 2 technicians and 1 admin officer. In addition, 3 staff are associated with the chemical biology screening facility and contribute to laboratory activities. The science is strong and the group leader is internationally recognised for his work in signal transduction and translational research. There is a strong commitment to translational research, with 5 active studies (including an interventional trial in HIV). The PI is to be congratulated for his capacity to lead the institution, participate in multiple international networks (e.g., FP7 EU-OPENSCREEN; EATRIS), and serve as lead scientific investigator on interventional clinical trials.

- ***Assessment of the scientific quality (in an international context; contributions to their field, scientific production and impact; national/international collaborations)***

The principal investigator (PI) has had a long-term commitment to the study of cAMP-dependent protein kinase (PKA) in T cells. His research group (prior to moving to the NCMM) discovered that PKA activates the kinase Csk as a signalling mechanism to account for the negative regulation of the TCR. Over the last decade, he has contributed to the integration of PKA and A kinase anchoring proteins (e.g., ezrin). Along the way, he has integrated exciting leading-edge profiling technologies, including mass-spec and phospho-flow cytometry based approaches for the study and validation of measured phosphorylation events, stimulated by immune modulatory ligands (e.g., PGE_2) (Blood 2010). Recently, he has reported the development of a mouse with a disrupted PKA anchoring domain, which exhibits hyper-activation of T cells; this study supported the model for ezrin anchoring of PKA and illustrated how modulating cAMP signalling may be used to control a mouse retrovirus (JI 2011). This line of scientific investigation was considered to be innovative and unique.

Translational research opportunities include studies on HIV – the group has published results from an exploratory study showing that COX-2 inhibitors can enhance markers associated with improved T cell immunity (*J Vir* 2011). For colorectal cancer, observation studies have associated PGE_2 levels, regulatory T cells and outcome to standard treatment (*Mol Cancer* 2012). The commitment to translation was seen as impressive and the committee looks forward to see future high impact publications originating from this group.

- ***Assessment of the translational research potential (in an international context; contributions to their field, scientific production and impact; national/international collaborations)***

The group has invested heavily in translational research activities and has significant international visibility (e.g., participation in EATRIS, OPENSCREEN, etc.). It is also clear from on-going collaborations, and group organization, that clinicians are involved in the research activities. The work on HIV-1 and COX-2 inhibitors is the most advanced (entering Phase IIa), but it was unclear to the committee if the infrastructure for qualified and validated immune monitoring, run in an ISO-15189 certified facility, is yet in place. This is important given that some of the endpoints for the trial are surrogate immunologic endpoints (e.g., CD38 expression).

- ***Assessment of the mentoring & training environment***

The environment for training is exceptional. Students and post-doctoral fellows from the group have access to training in 'high-end' technologies and have good access to clinical samples and experts knowledgeable in translational research. While busy, the group leader is present in the lab and works collaboratively on paper writing and presentations. Mentoring opportunities at the level of the institution are discussed elsewhere, but clearly the Centre will be looking to the group leader's lab for taking a leadership role in these group activities.

- ***Conclusions and recommendations***

The committee was impressed by the level of research and the infrastructure for discovery and translational research. The group should concentrate on exploiting its extensive resources and translational potential. While it should be considered an informal score, as the committee did not have ample time to fully evaluate the group, we ranked the group as *Excellent* / *Very Good*.

Founding group – Stem cell signalling

- ***Short description of the group (facts and organisation)***

This PI is a founder group leader. He has a stable group with little recent turnover or new recruitments over the last reporting period. Early in his career, the group leader made significant discoveries related to the Wnt signalling pathway, with the notable discovery of Shh in 1993. Currently, the group is focused on generation and characterization of Tankyrase inhibitors – as tool compounds (and perhaps drugs), which may have utility in cancer and/or stem cell differentiation. Other projects include the study of β-catenin and p120ctn, and other armadillo proteins in the context of cancer.

- ***Assessment of the scientific quality (in an international context; contributions to their field, scientific production and impact; national/international collaborations)***

This is an experienced investigator who is now making progress using chemical biology and chemistry collaborations to perform discovery science. This work has led to papers in *Cancer Research* (2012, 2013) *J Med Chem* (2012), and others. His recent track record is solid, but not outstanding. The compound generated seems to be a promising Tankyrase inhibitor. He has robust collaborations within the Centre, although the group does not receive significant funding from the NCMM. Perhaps related to the minimal financing, the PI is not very involved in the management or running of the Centre. Somewhat in contradiction with his lack of participation in the NCMM leadership, during discussion with the committee, he expressed frustration for having to re-locate away from the NCMM, presumably out-with his control.

- ***Assessment of the translational research potential (in an international context; contributions to their field, scientific production and impact; national/international collaborations)***

There is clear translational opportunities for the Tankyrase inhibitors.

- ***Assessment of the mentoring & training environment***

The committee was not given sufficient information to assess the training environment within the laboratory or the investigators contribution to the NCMM community.

- ***Conclusions and recommendations***

Based on the lack of enthusiasm and the limited contribution to Centre leadership, the committee could not see any added value in maintaing a formal relationship between the research group and the NCMM. While it should be considered an informal score, as the committee did not have ample time to fully evaluate the group, we ranked the group as *Good* and hope that the group is successful with the challenge of exploiting their exciting identification of an inhibitor of Tankyrase.

Founding group – Laboratory for molecular neuroscience

- ***Short description of the group (facts and organisation)***

The PI has been a group leader at NCMM since 2009. He was previously a senior scientist in Ottersen's research group. The Laboratory for molecular neuroscience (LMN) is one of the founding groups at NCMM, but Ottersen gave up his post when named the rector of UiO. The group leader currently holds a position as a professor of Medicine (2012-present).

- ***Assessment of the scientific quality (in an international context; contributions to their field, scientific production and impact; national/international collaborations)***

The group has since long conducted highly productive and leading research in Norway. A strong effort since the end of the 1990's focused on the role of aquaporins in the brain. A number of key findings have been made. The group identified AQP4 as a key aquaporin in the brain. For example, AQP4 is expressed in glial cell endfeet abutting the brain vasculature, has been associated with the development of oedema and AQP4 function is linked to epilepsy. The newly appointed PI has been a scientist in the lab during these developments, and has been instrumental in several of the key discoveries. Together with Ottersen, he was the author of an influential review in *Nature Rev Neurosci*, 2003, which describes the functions of aquaporins in brain.

Since taking over the responsibility in 2009, the group has continued to be productive. They have published results exploring how inhibitors of Na^+-K^+-2xCl^- co-transporter and Vasopressin receptor affects post stroke brain oedema, a drug candidate that can bind and block AQP4 has been identified and the group recently published the characterization of a complex including AQP4 and TRPV4. Interestingly, AQP4 and TRPV4 may be part of a bigger complex that regulates brain volume adjustments in response to osmotic changes (*PNAS*, 2011). In contrast to what has been seen in post-ischemic stress, this group found (in collaboration with Peter Agre) that AQP4, protects against

oedema in a murine model of cerebral malaria. Aquaporins in heart disease has also been a focus in two recent studies (*Basic Res Cardiol*, 2012; *J Mol Cell Cardiol.*, 2012). The significance of astrocyte polarity in disease, including epilepsy and Alzheimer's disease, has also been investigated. Finally, a focus on yet another aquaporin (AQP9) is of interest to the group, who published that AQP9 is expressed within dopamine neurons, suggesting the possibility that it is somehow implicated in Parkinson's disease.

Future plans seem to focus on three main areas: (i) mechanisms underlying loss of astrocyte polarity; (ii) identification and characterization of the osmosensing/volume regulating complex in the brain; and (iii) understanding the significance of AQP9 in Parkinson's disease. It was a bit difficult to know how the work will be continued with a new PI taking over the responsibility of Ottersen. It seems critically important for the new group leader to find his own focus, and avoid pursuing projects in too many directions.

The group has several ongoing collaborations with members at NCMM, including the glial-vascular imaging group and the membrane transport group on the interaction of AQP with TRPV4. Plans to interact with the Signalling Networks group at a later stage in this project were discussed. Collaborations with clinical groups are also reported and the group is engaged in a number of international collaborations (e.g. Peter Agre). The group has been productive with publications in high impact scientific journals. The studies published in *PNAS* on AQP4/TRPV4 complexes has attracted citations, and collaborative work on AQP4 in cerebral malaria appears to be an important new development in this field. In sum, productivity is impressive with numerous publications in good journals.

- ***Assessment of the translational research potential (in an international context; contributions to their field, scientific production and impact; national/international collaborations***

The work from this group has considerable translational potential and is largely oriented towards understanding and treating important neurological disorders. The results have identified AQP4 as a potentially therapeutic target in treatment of oedema. To this end, work is directed at synthesizing AQP4 blockers for validating AQP4 as a therapeutic target. Results relating to the development of epilepsy, heart disorder and Parkinson's disease are additional new developments with translational potential. As mentioned, the group maintains close ties with several clinical collaborators.

- ***Assessment of the mentoring & training environment***

The lab has a proven track record of research training, and this will likely continue. However, it is important to monitor carefully how the environment for education and supervision will develop with this leader as the new director of the research team.

- ***Conclusions and recommendations***

The committee recommends that NCMM carefully considers and defines the roles played by the founding partners. With the Associate Investigator program, NCMM has now acquired excellent young investigators, and a mechanism for mentoring and supporting staff, including via excellent collaborators. With this program now established, it remains somewhat unclear what the value of maintaining the “founding partner” status of the three original groups. Instead, when NCMM finds that local research groups provide added value and compatibility to NCMM, they may become involved with the the centre as Adjunct Faculty. The involvement of this founding group in NCMM should be considered in this context. While it should be considered an informal score, as the committee did not have ample time to fully evaluate the group, we ranked the group as *Very Good* and hope that the group leaders rises to the challenge of leading the LMN group.

Glial-vascular imaging group

- ***Short description of the group (facts and organisation)***

The PI has been a group leader at NCMM since 2009. He was recruited to NCMM from the University of Rochester, New York, where he performed his post-doc and currently holds a position as Adjunct Faculty. The group is now relatively large, with over 10 group members. Funding exceeds 8M NOK per year. The group leader is also the head of Letten Centre, an imaging two-photon laser scanning microscopy facility at the neighbouring Institute of Basic Medical Sciences (IMB), which is embedded within his own research laboratory. The PI is affiliated with UiO, Department of Neurology where he has an adjunct position. He maintains a productive collaboration with Nedergaard and co-workers at the URMC, Rochester, New York. The group leader has recently been appointed Professor of Medicine at the Department of Physiology, possibly complicating his continued participation as an NCMM group leader.

- ***Assessment of the scientific quality (in an international context; contributions to their field, scientific production and impact; national/international collaborations)***

The Glial-vascular imaging group focuses on glial cell biology and primarily utilises two-photon laser scanning microscopy as their principal technology. The group has established a very productive research program at NCMM since arriving in 2009. The research is focused on the function of astrocytes and aquaporin-4 (AQP4) in the function of the CNS. Together with Ottersen, the group leader showed in the late 1990's that AQP4 is mainly expressed in glial endfeet at the brain-blood interface. This important finding has continued to be a central focus in the group leader's independent research. In the last few years, the group has published data on the function AQP4 in Ca^{2+}-signalling in glial cells. They have demonstrated that endothelial cells are devoid of AQP4, a finding that has potential implications for the development of treatment of oedema with AQP4 inhibitors. Another important finding was that AQP4 is important for waste clearance from the brain glia-vascular pathway that probably serves similar functions as the lymph system in peripheral tissues.

Another line of research has focused on characterization of Kir4.1 potassium channels, which were also found to be co-localised with AQP4 at glial cell endfeet. The group has linked single nucleotide polymorphisms in the human Kir4.1 gene to mesial temporal lobe epilepsy and also provided mechanistic insight of relevance for this disorder.

The group has in recent years been productive with several publications in good journals. The publication in PNAS showing that AQP4 is linked to Ca^{2+} astrocyte signalling is a very important new development that has already received attention and numerous citations. This work was highlighted in *Nat Rev Neurosci*. Other developments have also been interesting. It has previously been established that AQP4 knockout reduces brain oedema, and now a new publication in PNAS used glial cell-specific conditional knockout to show that the effect can be ascribed to AQP4 expression in this cell type. Moreover, the publications linking Kir4.1 loss-of-expression and function in hippocampus glia to epilepsy provide additional exciting findings published recently by this group.

Overall the output of the research group is impressive, most notably recognised by its readiness to tackle important problems with their exciting new technologies, including intra-vital imaging through cranial observation windows. Specifically, the group leader has acquired a unique expertise at University of Rochester in two-photon intra-vital brain imaging and he has successfully established the methodology at UiO. It is impressive and they have established the possibility to image the brain of live animals. This now provides the basis for his independent research. A number of national and international collaborations are reported. These include the former mentor, Ottersen as well as other NCMM groups, including the Membrane Transport (structural biology) group. Several collaborations with Nedergaard's group at Rochester have resulted in important publications, including the finding that on AQP4 and Ca2+ signalling published in *PNAS*. The PI is also an adjunct assistant professor in Nedergaard's department and he co-supervises two of the group's PhD students. This is clearly a very important on-going collaboration.

- ***Assessment of the translational research potential (in an international context; contributions to their field, scientific production and impact; national/international collaborations)***

The group has established close collaborations with clinical departments at OiU. The science may have important clinical potential and a pathway to translation is clear. The work has important implications for understanding the basis of oedema after various insults and the identification of a paravascular waste transport mechanism is another exciting area with potential clinical implications (e.g., Alzheimer's disease).

- ***Assessment of the mentoring & training environment***

The group has graduated one PhD student and several others are close to finalizing their studies. The group consists of a mix of both graduate students and more senior associates and postdocs, and the environment for research training appears to be excellent. Members of the group did, however, comment on feeling disconnected from the NCMM community due to the distance between their lab and the centre, which is a pity.

- ***Conclusions and recommendations***

This group leader appears to be on an upward trajectory and it is anticipated that he will be successful in the coming years. The group has been able to establish an internationally competitive and highly interesting research program with considerable potential clinical significance. The committee concludes that the recruitment of this group leader to NCMM has been a success, further emphasised by the ability of the PI to successfully compete for external grant support. The recent promotion of the PI to Professor at IMB at the University of Oslo is an important measure of success. A major effort should be to maintain the positive influence of this group within the NCMM even after the PI assumes his professorial appointment, and it is therefore recommended that NCMM support this group leader as an Associate Investigator. While it should be considered an informal score, as the committee did not have ample time to fully evaluate the group, we ranked the group as *Excellent* and anticipate high-impact publications from the group in coming years.

Stem cell group

- ***Short description of the group (facts and organisation)***

This group was recruited in 2012 and has been going a year. There is already evidence of good projects focused on the molecular processes and regulators that underpin normal and malignant hematopoietic development and myeloproliferative disease / myelodysplastic syndromes (MPD / MDS). The research program is ambitious, well thought out and quite focused. Specifically, the PI will generate induced pluripotent stem cells (iPSC) from MDS blood cells and use them to study the activation of signalling pathways, epigenetic and genetic changes in MDS-iPSC and primary MDS blood samples. She will also try to differentiate MDS-iPSC into blood progenitors and use MDS-iPSC to screen shRNA libraries and small compounds that can reverse the block in *in vitro* blood cell differentiation. This should yield exciting hits and the PI is well placed to validate and pursue such hits. The second project is to generate / use genetic deletion in mice lacking ankyrin repeat and KH domain containing 1 protein (AnkHD1) – a putative regulator of the JAK-STAT pathway that is altered in human leukaemias. This is an interesting project, and the PI is well positioned to perform this line of research. As an early measure of success, they already have generated KO ES cells. The third project is a translational research project, run in collaboration with a clinician at UiO, with the aim to identify conditions that allow the expansion and genetic manipulation of human umbilical cord blood and adult bone marrow $CD34^+$ stem cells. Employing TALEN technology and transferring modified cells into NSG mice (generating humanised mouse models), the group will be in a position to examine the hematopoietic system. This is a challenging project, but if achieved, would be a major step forward for the field.

- ***Assessment of the scientific quality (in an international context; contributions to their field, scientific production and impact; national/international collaborations)***

As indicated above, the PI has a focused and well thought out research plan. The committee agreed that this was an excellent hire (top CV and exciting research project), and that the group leader is

proposing a balanced and sensible program that is expected yield exciting and important results. She is obviously aware of the need to publish (as stated) and she has the ambition for high profile journals – this is excellent. Local and international collaborations are in place, which include partners that provide access to clinical samples.

- ***Assessment of the translational research potential (in an international context; contributions to their field, scientific production and impact; national/international collaborations)***

There is a strong disease focus to the research, as discussed above. Two of the three projects utilise human subject materials and the proposed work has a high likelihood to result in discoveries that can be applied to the management of MDS / MPD.

- ***Assessment of the mentoring & training environment***

The committee was not provided sufficient information to assess the training environment of this new laboratory. What was clear is that the PI is engaged, works in the lab herself, and that there was good communication in the group.

- ***Conclusions and recommendations***

We believe that the PI has a mature research plan and that the likelihood of success is high. We encourage the leadership of the NCMM to provide strong mentorship and encouragement with respect to grant writing (in particular, application for a starting ERC grant). While it should be considered an informal score, as the committee did not have ample time to fully evaluate the group, we ranked the group as *Excellent* for the potential that we see in this new group and young group leader.

Prostate cancer group

- ***Short description of the group (facts and organisation)***

The group was created in 2010, with the PI coming from the UK where the group leader made important contributions to the field of prostate cancer genomics. The group is composed of 6-7 investigators, including three PhD fellows and two post-docs. The committee had the opportunity to visit the laboratory, which was well organised and equipped. Specifically, the team has access to a conventional qPCR machine and a robotic system for performing chromatin immunoprecipitation (ChIP). Sequencing data is outsourced to the Norwegian Sequencing Facility. The group has identified adequate strategies for data analysis and a seemingly talented (and confident) post-doctoral fellow has acquired bioinformatics skills that support the group's activities. While the committee did not have access to the recently published papers, we were informed that the group has had acceptance of two manuscripts in which the group leader is the senior author – one in *PLoS One* and the other in *Cancer Research*. This is a solid start.

- ***Assessment of the scientific quality (in an international context; contributions to their field, scientific production and impact; national/international collaborations)***

It is challenging to assess the scientific quality of the group based on the materials that were provided to the committee. This is in part due to the limited output of studies originating from NCMM. Objectively, the research group has been successful in raising funds – grant support coming from two EU projects and Norwegian National foundations. Additionally, the infrastructure put in place seems adequate and the attention to limiting pre-analytic bias in preparation of materials for ChIP-Seq and ChIP-on-chip analysis was appreciated. Access to clinical samples does not appear to be limiting and the group has taken advantage of available local and international Biobanks. The presentation focused on one project related to androgen receptor mediated changes in metabolic pathways, which appear perturbed in the context of prostate cancer. Three pathways are being explored: unfolded protein response pathway, autophagy and modulation of the hexosamine biosynthetic pathway (the latter being discussed in great detail). The committee recommends that the group concentrate on defining the interplay between these pathways and the identification of the multiple hits (as well as ordering of

events) that result in early phases of tumorigenesis. Additionally, it behoves the investigators to integrate their ideas of cell stress with the extensive body of knowledge on cell death pathways.

- ***Assessment of the translational research potential (in an international context; contributions to their field, scientific production and impact; national/international collaborations)***

There is a clear translational commitment exhibited by the research group and the group leader. This was greatly appreciated and in reading the several reviews written by the group leader (esp., *Sci Transl Medicine*), it is clear that this is a passion and long-term investment. Objectively, this could also be noted by the organization of the scientific work, the efforts made to build relationships with existing Biobanks and the launching of new observational studies. The group has initiated some important collaborations with other investigators within the Nordic EMBL partner institutions. Additionally, there is evidence of networking activities with other investigators examining prostate cancer GWAS; and collaborations with investigators performing interventional vaccine trials. There is significant potential for the translational research and the attention to pre-analytic error will ensure the possibility of clinical application.

- ***Assessment of the mentoring & training environment***

The committee greatly appreciated the spirit and openness of the group leader, as well as the dynamism of the members of the lab with whom we met. In particular, we noted the collegial spirit and the readiness to support other NCMM groups in optimizing and utilizing ChIP based strategies in their research efforts.

- ***Conclusions and recommendations***

The evaluation committee agrees with the SAB 2013 report that the group leader be cautious in establishing a clear focus for the lab – the scientific presentation demonstrated that this message was effectively communicated – but looking at the report and a cursory discussion of other activities indicate that prioritization or research topics and integration of the disparate cell biologic, biochemical, genomic and metabolic findings is still required. While it should be considered an informal score, as the committee did not have ample time to fully evaluate the group, we ranked the group as *Very Good,* with the potential to achieve scientific and translational research excellence in the coming years. This new PI needs to find his own niche in a very competitive area if he is to have impact, and the senior management should monitor progress and advise.

Breast cancer group

- ***Short description of the group (facts and organisation)***

The group leader was recruited in 2011 with the aim to address the determinants of response to anti-ER and anti-HER2 therapies, translating discoveries, where possible, to the clinic. A long-term aim is to develop mouse models as pre-clinical tools – although how this would be done was not detailed. Sub-aims centre on regulation of FOXA1 and how this is regulated (e.g., its binding to chromatin) by upstream signalling in different breast cancer contexts. The translational ambition is that this will help identify new targets to interfere with FOXA1 function. In addition, the PI will address the function of the FOXA1/TLE1 complex in cells when key cell signalling pathways are repressed (although again the reasons why this will be pursued and how this will be achieved is not fleshed out, nor is it clearly stated). A final project is aimed at establishing a mathematical model that defines the network of changes that link disease status and clinical outcome.

- ***Assessment of the scientific quality (in an international context; contributions to their field, scientific production and impact; national/international collaborations)***

The track record of this young investigator prior to starting his lab was excellent and his recruitment to NCMM was expected to strengthen cancer genomics within the centre. While it is too early to assess

objective output from this new independent group, the committee was concerned about the presentation of the work and the ability of the group leader to defend the stated aims and to prioritize. The research program is diffuse, overly ambitious (in a hugely competitive field) and unfocussed. The scientific rationale was not well explained, neither in the written report nor the oral presentations. Moreover, the responses to questions asked were not always adequately addressed. Mentors supporting this group leader need to help focus the research goals in a way that leads to objective outputs (i.e., papers) within the allotted time. The committee also expressed concern that applications for competitive grants be used to clarify ongoing work, rather than propose new research projects (e.g., work on FoxA1 in endometrial cancer). Finally, it was not clear to the committee whether the PI has experience of generating mathematical models of expression profiles that could define a link between breast cancer phenotypes and/or clinical outcome. This PI has a lot of potential if supported and provided with adequate advise and mentoring.

- ***Assessment of the translational research potential (in an international context; contributions to their field, scientific production and impact; national/international collaborations)***

Translation is aimed at identifying predictive biomarkers, or signatures, of response of different types of breast cancer to tamoxifen. This is a competitive area – many (bigger) groups / consortia are pursuing this in breast cancer. One question is whether transcription factors and gene expression will produce the answers or whether NGS will be required to deepen the analysis. Time will tell, but this young investigator has a chance of making a significant contribution if he remains focused in his questions and careful about forging international collaborations.

- ***Assessment of the mentoring & training environment***

The committee was not provided with sufficient information to assess the training environment of this new laboratory. It seems that good collaborations are in place already within the NCMM and a nice partnership exists with the Prostate Cancer research group.

- ***Conclusions and recommendations***

While it should be considered an informal score, as the committee did not have ample time to fully evaluate the group, we ranked the group as *Good* for the presentation of the work and ability to defend the project to the committee, and *Very Good* for future potential, if the group leader rises to the challenge of leading a competitive research group. Mentorship will be critical and we call upon the NCMM to define a clear monitoring and mentoring plan.

Membrane transport group

- ***Short description of the group (facts and organisation)***

The group leader was recruited to NCMM in 2010 from a position as an Associate Professor at Aarhus University, Denmark. He was originally trained in structural biology at the EMBL Outstation in Hamburg. The PI is affiliated with the Institute for Experimental Medical Research, Oslo. The group currently consists of 6-7 investigators (PhD student, postdocs and MSc students) and 1 technician.

- ***Assessment of the scientific quality (in an international context; contributions to their field, scientific production and impact; national/international collaborations)***

The Membrane transport group is using structural biology to address important problems in membrane biology with focus on pH homeostasis in the pathogenic virulence system mgtBC and mgtA. The group leader has previously done excellent work on P-type ATPases. In 2007 the PI was the first author on a study (*Nature*, 2007) that has been highly cited. Highlighted on the cover of the journal, the study described the P-type ATPase Ca^{2+} pump, a recognised highlight of the year in structural biology. Recent progress includes solving the structure of Lmo0818, a P-type ATPase expressed by *Listeria monoctyogenes*. The line of research has continued at NCMM in parallel with a number of other collaborative projects. The structural studies have the potential to inform drug development, especially relevant for design of drugs targeting pH-dependent virulence factors in studied pathogens

(e.g., Salmonella). In a collaborative project, the crystal structure of SSSCA1 has been solved. SSSCA1 is an autoantigen expressed in patients with the autoimmune disease Sjögren's syndrome and new data links the function of SSSCA1 to Wnt signalling and cell cycle control. This approach is also being exploited for the purpose of drug development by a new biotechnology company in Oslo. In yet another project, the group is examining the structural aspects of isatin (1H-indole-2,3-dione), a compound with inhibitory effects on monoamine oxidases. There have been a couple of reports indicating that isatin is increased in urine in patients with Parkinson's disease. The group aims at developing a new assay for enzymatic detection of isatin by using bacterial isatin hydrolase. The long-term aim is to develop a novel biomarker assay for Parkinson's disease. Perhaps due to lack of detail and literature supporting the link between increased isatin and Parkinson's disease, the committee was unconvinced by the strategy here.

The group leader has published several important studies in his career, and this looks to continue. The PI is the first author on a review in *Nat Rev Mol Cell Biol*. Moreover, he has published a senior author paper on plasminogen activator inhibitor-1 (*J Biol Chem*, 2011). Since 2008 he is an author on a total of 16 collaborative papers.

The group seems to be a positive influence on the collaborative environment at NCMM, and is now actively engaged in collaborations with several other labs. It is also significant that this recruitment has brought a first membrane structural biology lab to Norway. The group has also successfully competed for outside grants and its total spending for 2012 amounts to 6MNOK.

- ***Assessment of the translational research potential (in an international context; contributions to their field, scientific production and impact; national/international collaborations)***

While more oriented towards the fundamental research, the projects that drive the group's structural biology research have medical relevance (e.g., defining drug targets for Salmonella infection in chickens, understanding the interaction between Tankyrase and SSSCA1). Stronger (and possibly independent) evaluation of the clinical questions may be valuable in order to help prioritise some of the ongoing collaborations.

- ***Assessment of the mentoring & training environment***

The committee was not provided sufficient information to assess the training environment of this new laboratory. It seems that good collaborations are in place already within centre and a nice partnership exists with the stem cell signalling research group.

- ***Conclusions and recommendations***

The group leader is a highly successful structural biologist and an excellent recruitment for NCMM. Almost all previous papers have been published together with his previous mentor at Aarhus University and it will now be critical for the PI to establish an independent track record for his structural biology lab at NCMM. We anticipate this will be forthcoming. Considering the many collaborations that have already been initiated, it seems likely that a successful line of investigations will continue, but it will be important to define his leadership role (ownership) on some of these studies. In other words, a key issue for the PI will be to maintain a strong focus on his own research interest, while contributing his active collaborations within and outside Norway. While it should be considered an informal score, as the committee did not have ample time to fully evaluate the group, we ranked the group as *Very good with the potential to achieve Excellent in coming years*. As with other new PIs, we advise careful monitoring and mentoring for this investigator.

E. Conclusions and recommendations

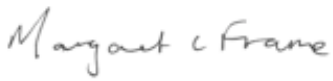
The committee ranks the NCMM as *Very Good*, highlighting that its basic and translational research demonstrate a high degree of originality, but falling a little short of the highest standards of excellence on the international stage. This is to be expected five years into the program, and the committee was impressed with the progress made thus far. The publication profile, while still hard to measure at an

early time point in the centre's growth and development, is impressive. Nonetheless, given the resources provided the committee would expect to see the numbers of high-impact publications increasing in the coming years. The efforts in capacity building (technical platforms for innovative discovery science) were excellent, and the translational research objectives are important and will yield success in years to come. Training activities are evolving in a good way, but more can be done to establish a coherent training environment that inspires the next generation of research leaders in Norway, and prioritises the continued medical education of collaborating clinical teams, while exposing basic scientists to high-priority medical questions. The leadership by the director was seen as excellent, but we do think he is over-committed and needs senior colleagues with whom he can share the load. The committee recommends the continuation of funding support from the Research Counsil (and also the other stakeholders that participated in the creation of the NCMM). If possible, the committee advises that additional funds be made available, earmarking monies for the hiring of 1-2 senior group leaders and capacity building in the area of bioinformatics and/or computational science, recognising all these suggestions would require further investment.

Finally, the committee wishes to comment on its support for the NCMM translational vision. The NCMM, with careful strategic planning, can be enormously successful in pursuing its translational objectives for the benefit of patients. It is ideally placed to bridge basic biology knowledge and discovery science for unmet clinical need. However, changing patient care does not happen overnight, and is the responsibility of an intricate patchwork of scientists, clinicians, biotech, industry, political activists, policy makers, insurance providers and governmental regulatory agencies. Importantly, the NCMM should be allowed the time to realise its translational ambitions through quality science and clinical collaboration. If the stakeholders wish to ensure delivery of new diagnostic strategies and therapeutic treatments to patients, they must continue their investment, with a shared commitment to support NCMM and work together to optimise translational opportunities. In particular, we highlight the need for streamlining regulatory procedures that protect individuals while making clinical trial testing efficient, supporting the building of ISO-15189 certified platforms for monitoring patient samples during clinical trials, and establishing mutually beneficial opportunities for academic labs to partner with industry on biomarker and drug development. In light of these comments, we express our belief that all partners must support the NCMM, helping to nurture Norwegian scientific excellence and translational outputs for patient benefit in the long term. Anything else would be to miss a great opportunity and lose the benefits of investments made over the last five years. This must be supported.

Committee member signatures

Matthew L. Albert, MD PhD
Director, Department of Immunology
Founder and co-Director, *Centre d'Immunologie Humaine*
Professor and Head of Laboratory of Dendritic Cell Biology
Institut Pasteur, Paris & Inserm U818



Margaret C Frame BSc PhD FRSE FMed Sci
Professor of Cancer Research
Director of Research, College of Medicine and Veterinary Medicine
University of Edinburgh, Edinburgh, UK.

Thomas Perlmann, PhD
Professor of Molecular Developmental Biology
Director of the Ludwig Institute, Stockholm Branch
Karolinska Institutet, Stockholm, Sweden

Annex

1. **Framework for the evaluation and Mandate**
2. **Schedule for NCMM site visit, May 6th 2013**
3. **Schedule for Evaluation of the NCMM, May 7th 2013**
4. **Biographical sketches for Evaluation Committee**

Evaluation of the *Centre for Molecular Medicine Norway (NCMM)*

Framework for the evaluation and Mandate

1. Framework for the evaluation

1.1 Introduction

EMBL (European Molecular Biology Laboratory) is the leading European institution in molecular life sciences. The idea to establish Nordic EMBL-affiliated Centers for Molecular Medicine was generated by EMBL Council delegates from the Nordic countries, and strongly supported by Nordic Research Councils.
The initiative resulted in the EMBL Partnership Agreement between universities in Norway, Sweden and Finland and EMBL, and was signed in 2007. The purpose of this agreement is to facilitate scientific collaboration, and thereby capitalize on both intellectual and material resources within the Nordic region in order to exploit emerging technologies and to develop molecular and personalized medicine. The NCMM was formally established in October of 2008 and, together with the Finnish Institute for Molecular Medicine (FIMM, University of Helsinki) and the Laboratory for Molecular Infection Medicine Sweden (MIMS, Umeå University), constitute the Nordic EMBL Partnership for Molecular Medicine.

The Research Council of Norway (RCN) based the selection of a national center on the open competition arena for Nordic Centre of Excellence within molecular medicine, where the three Norwegian finalists formed the core of the national center, and was called Centre for Molecular Medicine Norway, NCMM.

The NCMM is a joint venture among the University of Oslo (hosting institution), the Research Council of Norway (RCN) and South-Eastern Norway Regional Health Authority (Helse Sør-Øst RHF). The centre is partly financed by the RCN for a 5-year period, with a total allocation of NOK 50,000,000. Due to some delay in recruiting group leaders, the end of the present center period has been postponed to December 2014.

NCMM is an international biomedical research institute with the overall objective of translating basic medical research into clinical practice. NCMM is particularly focused on disease mechanisms where Norway has clear strengths, including non-communicable diseases such as cancer, cardiovascular disease, CNS-related disease and immune disorders. By establishing new diagnostic methods and identifying potential drug targets, as well as adapting medical technologies for more patient-specific applications, the NCMM is developing new therapeutic strategies for commercial exploitation.

The centre’s location in the Oslo Research Park results in overlap and co-localization with the Biotechnology Centre of Oslo and the Centre for Molecular Biology and Neuroscience.
The center started with three founding groups and has expanded with five new groups with internationally recruited young scientists as group leaders.

The center is headed by a director. The local Board, which was established to coordinate the interactions with local partners, is responsible for initiating NCMM activities and, in collaboration with the Director, for ensuring the Centre’s overall coordination and progress – its national mandate to facilitate translational research in Norway.

The National Reference Group, appointed by Research Council of Norway, has responsibility for national coordination and for ensuring that other regions can benefit from the academic and recruitment opportunities represented by the EMBL node. In addition the NCMM has a Scientific

Advisory Board (SAB) which was appointed by the Board in June, 2011. The SAB is to investigate the scientific performance and to advise on the further development of NCMM.

In the contract between the RCN, the South-Eastern Norway Regional Health Authority and University of Oslo, it is specified that funding for the next five-year period is based on a satisfactory mid-way evaluation of the center performed after four years. The evaluation will be carried out in 2013.

1.2 Purpose of the evaluation

The purpose of the evaluation is to assess the scientific quality of the research conducted in the center, and to assess the strategic role and development of the center in the context of being a research center within molecular medicine and translational research in Norway. Furthermore, the evaluation should provide recommendations for further development of the center.

The evaluation of the NCMM will provide data to underpin the decision as to whether an extension of the center allocation for a new five-year period is recommended.

1.3 Organization

The evaluation will be carried out by an international Evaluation Committee. The Evaluation Committee should base its evaluation on the written material provided, as well as a hearing and a site visit to the center. The Evaluation Committee will present its findings and recommendations in a written report.

1.4 Background material for the evaluation

- Contract between the RCN, University of Oslo and the South-Eastern Norway Regional Health Authority,
- The project description *Plan for the establishment of Centre for molecular Medicine Norway – Nordic EMBL Partnership, revised March 2008.*
- Agreement between EMBL and the three Nordic nodes for establishing the Nordic EMBL Partnership for molecular medicine.
- Self-evaluation and Fact sheet from the center, as well as Self-evaluations and CVs from the individual groups, according to a standardized outline
- Report from the NCMM Scientific Advisory Board from 2012
- Assessment from the University of Oslo
- The centre's annual reports from 2009 & 2010 and 2011

2. Mandate for the Evaluation Committee

The evaluation of the center is to emphasize the following elements:

Scientific quality of research
The evaluation is expected to assess to what extent:

- the centre groups conduct research within molecular medicine and translational research at a high international level, as judged by the significance of contributions to their field, prominence, and scientific impact of their research
- the scientific production is of high international standard and whether the results currently being produced (e.g. number of articles published) are reasonable in terms of the resources available

- the centre groups are actively and successfully taking part in national and international research collaborations and networks, including strong links between basic and clinical research environments

Strategic role and development of the center
The evaluation is expected to assess to what extent:

- The EMBL partnership facilitates access to scientific infrastructure, including databases, facilities and instrumentation, as well as access to clinical materials, services and training activities provided by each of the partners.
- The Nordic partnership has built on and exploited the strengths in all three partner institutes.
- The centre is able to counteract fragmentation and build critical mass
- The centre has been able to attract and recruit outstanding younger scientists within molecular medicine nationally and from abroad
- The center has been successful in developing infrastructure to facilitate translation of discoveries in basic medical research into clinical practice
- The centre has exploited national scientific strengths
- The centre has contributed to training activities and competence development
- The centre has enhanced collaboration with biotechnology and bio-pharmaceutical industries
- The centre has established new contacts and created new research networks beneficial for national and international research within its field.
- The scientific leadership is being exercised in an appropriate way, at both centre and group level
- The centre's activities and organization contribute to the aim of being a national resource centre

Research plans for the next five-year period:
Further, the evaluation should assess whether the center has satisfactory strategic and practical plans for future development, including:

- scientific plans and priorities for providing science with high scientific impact and relevance with respect to the centre's goals
- recruitment and training
- collaboration and synergy between centre groups
- collaboration nationally/internationally/with EMBL-partners, including basic and clinical collaboration
- strategies for innovative findings of commercial interest
- strategy for its national role as a national resource centre

NCMM Midterm Evaluation – Site Visit May 6

Time schedule:

15.00	Arrival, access building
15.15-15.30	Short introduction about NCMM by Director Kjetil Taskén
15.30-16.15	Tour of NCMM facilities and adjoining Bio Core facilities Group Leaders and other staff available
16.15-17.00	Committee meeting with selected postdocs and students Coffee and round table discussion
17.00-17.15	Walk to the Preclinical Medicine building (Domus Medica)
17.15-17.45	Tour of Letten Centre/Nagelhus Group (Possibly also visit the labs of Amiry-Moghaddam and Krauss if time allows)

NCMM TOUR OF PREMISES:

Station 1) Preben Morth - fermentation, crystals etc.
Station 2) Judith Staerk - new stem cell labs
Station 3) Ian Mills - Chip-IP robot and more
Station 4) Toni Hurtado / Siv Gilfillan - tissue culture, incucyte and more
Station 5) Kjetil Taskén - BiO proteomics, microscopy, chemical biology facilities
(to the extent time allows)

Evaluation of the Centre for Molecular Medicine Norway - NCMM

Evaluation meeting 7th 2013

The Research Council of Norway, Stensberggata 26, Oslo

Day 2 – May 7th 2013 – Hearing		
08.30-09.00	Committee preparations for day 2	participants
09.00-09.45	Center presentation and hearing	Kjetil Tasken, center director Ragnhild Lothe ,chair of the board Elisa Bjørgo, CAO
10.00-11.10	Center groups – presentations and hearing	Founding partners: Kjetil Tasken, Stefan Krauss, Mahmood Amiry-Moghaddam
11.20-12.10	Center groups II – presentations and hearing	*Group 1 and 2* Erlend Nagelhus Judith Staerk
12.15-13.00	Lunch	
13.00-14.30	Center groups III – presentations and hearing	*Group 3 , 4 and 5* Ian G. Mills Jens Preben Morth Toni Hurtado
14.30-15.45	Committee discussion	
15.45-16.45	Center and relevant institutions	Tasken, Lothe and Bjørgo *HSØ:* Dir. Research and innov. T. Vaage, Research leader Ø. Kruger *University of Oslo:* Rector Ole Petter Ottersen MLS-leader Odd Stokke Gabrielsen, Vice dean Hilde Nebb,
16.45-17.15	Committee discussion – conclusion and next steps	

All group leaders will attend from 11.20 – 14.30 on May 7th.
Iain Mattaj (EMBL) and Chair of the national reference group will both attend as observers on May 7th.

Matthew L. Albert, MD PhD

Pr. Matthew Albert is an INSERM director of research and full professor working at Institut Pasteur, where he heads a mixed INSERM / Pasteur Unit. His current positions also include Director of the Department of Immunology; co-Director and Founder of The Center for Human Immunology at Institut Pasteur; and Adjunct Faculty at Cochin Hospital. He received his M.D. at Cornell University Medical College and his Ph.D. in Immunology at The Rockefeller University, under the direction of Prs. Robert Darnell and Nina Bhardwaj (in the laboratory of Pr. Ralph Steinman). He trained in Clinical Pathology at The New York Presbyterian Hospital and was a Clinical Scholar at The Rockefeller University Hospital, under the direction of Pr. Barry Coller.
Albert's laboratory is centered around a 'bedside-to-bench' approach to translational research. This has helped him to stay firmly rooted in clinically relevant scientific questions, which has furthered the understanding of disease pathogenesis and helped to establish the proper scientific foundation for the identification of new therapeutic interventions. Specifically, his basic science and clinical research goals focus on the characterization of the cellular and molecular mechanisms underlying the cross-priming of tumor and viral-specific cytolytic T lymphocytes (CTLs). He aims to: define the direct and indirect influence of apoptotic and autophagic cell death on immunity; identify mechanisms of tumor immunity in patients with superficial transitional cell carcinoma of the bladder; and characterize the complex role of type I IFNs and interferon stimulated genes (ISGs) in HCV disease pathogenesis and treatment.

Among the numerous awards, he has received the Burroughs Wellcome Fund Career Award, The Doris Duke Clinical Scientist Development Award and The European Research Council Young Investigator Starting Award. He is currently coordinating two program projects: (i) Spontaneous clearance in Patients acutely infected with HCV: *Immune profiling, Novel biomarkers and X-omics approaches* (the SPHINX Consortium); and (ii) MILIEU INTÉRIEUR: Defininig the genetic and environmental determinants of immune phenotype variance – establishing a path towards personalized medicine.

Active clinical studies (selected)

Principle Scientific Investigator. Cochin Hospital. Phase I interventional trial: Use of dipeptidylpeptidase IV (DPPIV) inhibitors for enhancing response to IFN-based therapy in patients with chronic HCV (co-PI: Stanislas POL).

Principle Scientific Investigator. Rouen CHU. Observational study: Effective Tumor Immunity in Transitional Cell Carcinoma of the Bladder (co-PI: Christian Pfister).

Principle Scientific Investigator. Cochin Hospital. Observational study: IP-10 as a biomarker for the response to therapy in chronic HCV patients (co-PI: Stanislas POL).

Investigator. Ain Shams Hospital and the Tropical Medicine Research Institute, Cairo Egypt. Cohort study: The immunopathogenesis of acute HCV. (co-PIs: Arnaud Fontanet, Gamel Esmat).

Margaret C Frame, PhD FRSE FMedSci

Margaret Frame graduated with a first class honours BSc in Biochemistry, followed by a PhD from the Medical Faculty, both at the University of Glasgow. She worked for a brief period in industry, and then joined the MRC Virology Unit in Glasgow as a post-doctoral scientist until 1987. After the arrival of three sons, she returned to work at the Beatson Institute for Cancer Research in 1992, first as a post-doc and then subsequently as a group leader. In 1996, Margaret was jointly appointed as Professor of Cancer Research in the Faculty of Medicine at the University of Glasgow and the Beatson Institute, where she became Deputy Director in 2002. She was awarded the Tenovus Medal in 1999 for her work on Src family kinases, was elected a Fellow of the Royal Society of Edinburgh in 2004, an EMBO Member in 2009 and a Fellow of the Academy of Medical Sciences in 2011.
Margaret Frame's long-held research interests are in cancer invasion and metastasis, and the role of tyrosine kinases in controlling tumour cell spread. She has a CR-UK funded program of research to work on understanding cancer invasion and metastasis, the key hallmarks of malignancy, and an ERC advanced investigator grant to build a new cancer discovery platform. A major goal is to work with clinicians treating breast, pancreatic and ovarian cancer to determine whether, and if so how, targeting the invasive and metastatic processes may be therapeutically beneficial, and may be monitored in the pre-clinical and clinical settings by novel imaging techniques.

Margaret joined the new Edinburgh Institute of Genetics and Molecular Medicine at the University of Edinburgh in October 2007. She co-directs the Edinburgh Cancer Research Centre in Edinburgh University's College of Medicine and Veterinary Medicine, with the role of Science Director in the recently established Cancer Research UK Centre (from January 2010). The vision of the Edinburgh Cancer Research Centre she directs is to develop novel and emerging technologies for the development of a new model for cancer discovery and translational science. Margaret has also recently taken up the post of Director of Research in the College of Medicine and Veterinary Medicine at the University of Edinburgh. She is Chair of Cancer Research UK's Career Development Panel, and serves on several funding panels and Advisory Boards in the UK and across Europe.

Thomas Perlmann, PhD

Professor
Ludwig Institute for Cancer Research; Karolinska Institute

Thomas Perlmann completed his undergraduate studies at Stockholm University and received his PhD from the Karolinska Institute, Stockholm, Sweden, in 1991. After postdoctoral work at the Salk Institute in San Diego Thomas Perlmann has been a faculty member of the Karolinska Institute. He currently holds a joint position at the Ludwig Institute for Cancer Research, Stockholm Branch and the Karolinska Institutet where he is a full Professor. The main research interest is in developmental neuroscience and stem cell biology. A main emphasis is directed at understanding how dopamine neurons develop. These are cells that are particularly vulnerable and degenerate in patients with Parkinson's disease. The group has elucidated a number of transcription factor pathways influencing the development and survival of mesencephalic dopamine cells. The understanding of dopamine neuron development has also enabled the group to develop novel strategies for the generation of specific neuron types from stem cells. The lab is also investigating how dopamine neuron transcription factors influence the maintenance of the dopaminergic system in the adult brain. These studies have resulted in new insights of relevance for the understanding of Parkinson's disease. Thomas Perlmann is a member of the Nobel Assembly at the Karolinska Institutet and of the Swedish Royal Academy of Sciences.

Selected publications

1. Panman, L., Andersson, L., Alekseenko, Z., Hedlund, E., Kee, N., Mong, J., Uhde, C.W., Deng, Q., Sandberg, R., Stanton, L.W., Ericson, J., **Perlmann, T.** (2011) " Transcription factor-induced lineage selection of stem cell-derived neural progenitor cells" Cell Stem Cell, 8, 663-675
2. Malewicz, M., Kadkhodaei, B., Kee, N. Volakakis, N. Hellman, U., Viktorsson, K., Leung, S.Y., Chen, B., Lewensohn, R., van Gent, D.C., Chen, D.J., **Perlmann, T.** (2011) "Essential Role for DNA-PK-mediated Phosphorylation of NR4A Nuclear Orphan Receptors in DNA Double Strand Break Repair", Genes Dev, 25, 2031-2040
3. Decressac, M., Kadkhodaei, B., Mattsson, B., Laguna, A., **Perlmann, T.,** Björklund, A. (2012). a-synuclein–induced down-regulation of Nurr1 disrupts GDNF signaling in nigral dopamine neurons. *Sci Transl Med,* 4: 156-163
4. Holmberg, J. and **Perlmann, T**. (2012) "Maintaining differentiated cell identity", Nature Reviews Genetics, 13, 429-439
5. Banafsheh Kadkhodaei, Alexandra Alvarsson, Nicoletta Schintu, Daniel Ramsköld, Nikolaos Volakakis, Eliza Joodmardi, Takashi Yoshitake, Jan Kehr, Mickael Decressac, Anders Björklund, Rickard Sandberg, Per Svenningsson, and **Thomas Perlmann** (2013). Transcription factor Nurr1 maintains fiber integrity and nuclear-encoded mitochondrial gene expression in dopamine neurons. *Proc. Natl. Sci., USA*, *110*, 2360–2365.